Delayed allergic skin reactions to vaccines

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ABSTRACT

Background: *Recent advances in vaccination against the severe acute respiratory syndrome coronavirus 2 pandemic have brought allergists and dermatologists to the forefront because both immediate and delayed hypersensitivity reactions have been reported.*

Objective: *This literature review focused on delayed reactions to vaccines, including possible causative agents and practical information on how to diagnose, evaluate with patch testing, and manage subsequent dose administration.*

Methods: *Currently published reviews and case reports in PubMed, along with data on vaccines from the Centers for Disease Control and Prevention web site. Relevant case reports and reviews that focused on delayed reactions to vaccines were selected.*

Results: *Most delayed hypersensitivity reactions to vaccines include cutaneous manifestations, which vary from local persistent pruritic nodules to systemic rashes. The onset is usually within a few days but can be delayed by weeks. Multiple excipients have been identified that have been implicated in delayed vaccine reactions, including thimerosal, formaldehyde, aluminum, antibiotics, and gelatin. Treatment with antihistamines, topical corticosteroids, or systemic corticosteroids alleviates symptoms in most patients. Such reactions are generally not contraindications to future vaccination. However, for more-severe reactions, patch testing for causative agents can be used to aid in diagnosis and approach further vaccination.*

Conclusion: *Delayed-type hypersensitivity reactions to vaccines are not uncommon. If needed, patch testing can be used to confirm agents, including antibiotics, formaldehyde, thimerosal, and aluminum. In most cases, delayed cutaneous reactions are not contraindications to further vaccine administration.*

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Vaccines have been critical in preventing previously fatal illnesses. Adverse reactions to vaccines are seen, which may be of an immediate or delayed nature. Delayed reactions occur hours to days after vaccination and have included large local reactions, eczematous dermatitis, persistent hard nodules, erythema multiforme, urticaria, serum sickness–like reactions, acute generalized exanthematous pustulosis (AGEP), angioedema, and local pruritic eruptions.[1–4] However, the onset of delayed-type hypersensitivity reactions (DTHR) can occur up to a few weeks later.[5] Persistent hard nodules are believed to be induced by inflammatory or irritant reactions to aluminum (an adjuvant).[6,7] Typically, DTHRs are not contraindications to booster vaccine doses and tend to be self-limited.[5] Rarely, severe delayed cutaneous eruptions can occur, and the responsible components may be encountered in situations other than vaccines that are given infrequently, including personal products and medications. Extracutaneous manifestations of vaccine reactions, including arthritis; arthralgias; joint swelling; Henoch-Schonlein purpura; serum sickness; and other renal, hematologic, and gastrointestinal manifestations, are rarer.[4]

Vaccines contain multiple components that include the specific antigen(s) of the infectious agent (part or entire organism, messenger RNA [mRNA], and/or inactivated toxins),[5] preservatives (to extend shelf life), stabilizers, residual media, adjuvants (to increase immunogenicity), unintentional contaminants, and antibiotics.[3,4,8] Vaccine reactions are more commonly associated with components other than the infectious agent.[5] Knowledge of these components is necessary to assess for causative agents and for risk estimation with future vaccination. Fortunately, most delayed reactions are not typically contraindications to further vaccination.[5]

CORONAVIRUS DISEASE 2019 VACCINES

Three coronavirus disease 2019 (COVID-19) vaccines have currently been approved in the United

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Table 1 **Coronavirus disease 2019 vaccines**

Components	Reported Delayed Cutaneous Reactions, yes/no
Moderna*	
SM-102, 1.93 mg	No
Polyethylene glycol 2000 dimyristoyl glycero, 1.93 mg	Yes#
Cholesterol, 1.93 mg	No
1,2-distearoyl-sn-glycero-3-phosphocholine, 1.93 mg	No
Tromethamine, 0.31 mg	Yes§
Tromethamine hydrochloride, 1.18 mg	Yes§
Acetic acid, 0.043 mg	No
Sodium acetate, 0.12 mg	No
Sucrose, 43.5 mg	No
Pfizer-BioNTech¶	
(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.43 mg	No
2 ([polyethylene glycol]-2000)-N,N-ditetradecylacetamide, 0.05 mg	Yes
1,2-distearoyl-sn-glycero-3-phosphocholine, 0.09 mg	No
Cholesterol, 0.2 mg	No
Potassium chloride, 0.01 mg	No
Monobasic potassium phosphate, 0.01 mg	No
Sodium chloride, 2.16 mg	No
Dibasic sodium phosphate dihydrate, 0.07 mg	No
Sucrose, 6 mg	No
Janssen (Johnson & Johnson)‖	
Citric acid monohydrate, 0.14 mg	Yes**
Trisodium citrate dihydrate, 2.02 mg	No
Ethanol, 0.04 mg	No
2-Hydroxypropyl-B-cyclodextrin, 25.50 mg	No
Polysorbate-80, 0.16 mg	No
Sodium chloride, 2.19 mg	No
Host cell proteins, <0.15 μg	No
Host cell DNA, <3 ng	No

**From Ref. 10.*
#From Refs. 16 and 18.
§From Ref. 28.
¶From Ref. 9.
‖From Ref. 12.
***From Ref. 27.*

States. The U.S. Food and Drug Administration approved emergency use authorization for the Pfizer-BioNTech (Comirnaty [Pfizer NY, NY, USA-Biontech-Mainz, Germany]) COVID-19 vaccine, now for ages ≥ 12 years, on December 11, 2020.[9] Full approval for the Pfizer-BioNTech COVID 19 vaccine was granted by the U.S. Food and Drug Administration on August 23, 2021, for patients ages ≥ 16 years. Emergency use authorization for the Moderna (Moderna Global Headquarters-Cambridge, MA, USA) COVID-19 vaccine for ages ≥ 18 years was granted on December 18, 2020.[10] The mechanism of action of both vaccines involves modified mRNA, which is prepared in lipids, which permits the entry of RNA into patients' cells, which causes expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S antigen spike protein.[9–11] Janssen Biotech, Inc. (Janseen Biotech Horsham, PA, USA) was granted approval for emergency use authorization on February 27, 2021, for a single-dose COVID-19 vaccine.[12] The mechanism of action involves a "recombinant replication–incompetent adenovirus serotype 26 vector," which contains DNA that codes for the SARS-CoV-2 S antigen spike protein.[13] The components of the available COVID-19 vaccines, along with reports of delayed reactions to these components, are listed in Table 1.

DELAYED REACTIONS TO THE SARS-CoV-2 mRNA VACCINES

Results of a recent trial showed that delayed large local injection-site reactions to the mRNA COVID-19 SARS-CoV-2 Moderna vaccine occurred in 0.8% of participants (244 participants) after the first dose and in 0.2% (68 participants) after the second dose.[11] Symptoms included erythema, induration, and tenderness, which typically resolved after 4–5 days.[11] Blumenthal *et al.*[14] published a series of 12 patients who developed delayed large local reactions to the mRNA-1273 vaccine, with an onset range of 4–11 days. These reactions occurred near the injection site. Symptom resolution occurred between 2 and 11 days (median, 6 days); the patients were treated with a mixture of antihistamines and topical and systemic corticosteroids.[14] All 12 patients received their second dose of the vaccine; 6 had no symptoms, 3 had milder symptoms, and 3 had similar symptoms.[14] Most patients received the vaccine on the opposite arm and were treated with short- or long-acting antihistamines as premedication. The onset of reactions after the second dose, when they occurred, was much sooner (median, day 2).

A series of 16 patients with delayed cutaneous reactions to the Moderna mRNA COVID vaccine also demonstrated similar findings.[15] Fifteen patients developed erythematous painful local reactions near the injection site a median of 7 days (range, 2–12 days) after injection that lasted a median of 5 days (range, 1–21 days); most were treated with topical corticosteroids, antihistamines, and cold compresses.[15] Eleven patients had a recurrence of similar symptoms with the second injection that occurred sooner, lasted a shorter period, and were treated similarly.[15] Although the exact mechanism of these symptoms is not yet well understood, both studies[14,15] report skin biopsy findings, which consisted of a perivascular and interstitial inflammatory infiltrate with lymphocytes and eosinophils suggestive of a DTHR. This phenomenon has been coined "COVID arm." Overall symptoms seem temporary and amenable to treatment. Patients' concern with regard to subsequent vaccination can be addressed with modest interventions, if any, that seem to ameliorate symptoms. A large local reaction that occurred after the administration of a mRNA COVID vaccine (Moderna) is displayed in Fig. 1.

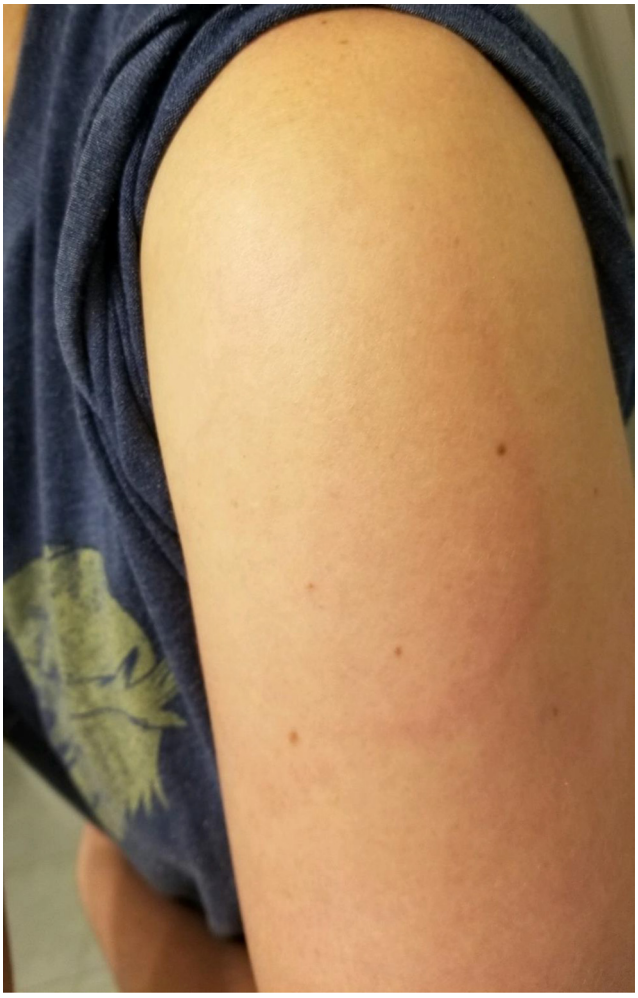

Figure 1. *Large local reaction 13 days after the first Moderna coronavirus disease (COVID-19) vaccine. This resolved within 24 hours without intervention. Of note, the individual did not develop this reaction after the second dose of the vaccine that was administered in the other arm. Photo courtesy of Lisa Bartnikas, M.D. Consent was obtained from the patient to publish this picture.*

COMPONENTS OF COVID VACCINES

Delayed reactions to many vaccine excipients are possible but polysorbates and polyethylene glycols (PEG) are now of particular interest because they are found in the available COVID-19 vaccines.

PEG

PEG has been in many classes of medications as well as in consumer products for decades; its molecular weight varies from 200 to 10,000 Da.[16,17] High-molecular-weight PEG is included in bowel preparations and methylprednisolone injections.[16] Lower-molecular-weight preparations include antimalarial medications.[16] Higher-molecular-weight PEG products are likely associated with anaphylaxis reactions, whereas lower molecular weights are associated with DTHR; although overall reactions to PEG are rare.[16] Contact dermatitis with positive patch testing (PT) has been associated with PEG in topical nitrofurazone, minoxidil, and corticosteroids.[18] PEG 400 was previously included in the North American Contact Dermatitis Group PT series,[18] with positive results most often found in patients with allergic contact dermatitis to nitrofurazone preparations. As use of this drug became less common, PEG 400 was removed from the North American Contact Dermatitis Group PT series.

Thirty-five of 836 patients (4.2%) had a PT to PEG 400 "as is" had a positive result, with more than a third of patients showing a late positive PT result starting on day 4 or later.[18] Therefore, it is important to plan day 7 readings for patients with a history of possible DTHR to PEG-containing vaccines. Other investigators report using the laxative solution BOHM (Laboratorios BOHM, Fuenlabrada, Spain), which contains PEG 4000 to PT for PEG.[19] PEG 400 is commercially available for PT from SmartPractice Canada (Calgary, Canada). Recently, a series of 26 patients with delayed reactions to the mRNA COVID vaccines, including large local reactions and exanthematous rashes, had a PT with PEG 400 1% in petrolatum, PEG 3350 10% in petrolatum PEG 3350 in aqueous solution, PEG 4000 10% in petrolatum, polysorbate 80 1% in petrolatum, and polysorbate 80 10% in petrolatum.[20] All PT results were negative in this series; patches were read at days 2 and 4.[20]

Polysorbate 80

Sorbitans are a family of emulsifiers derived from sorbitol and include sorbitan sesquioleate (SSO), sorbitan monooleate, and sorbitan monosterate. Polysorbates, which include polyoxyethylene-sorbitan-20-monooleate, also known as polysorbate 80 or Tween 80 and polysorbate 20, are fatty acid esters of polyoxythylene sorbitan. These substances can all potentially cross-react per the Contact Allergy Management Plan from the American Contact Dermatitis Society (www.contactderm.org).[21] Polysorbate 80 is structurally related to PEG and is a solubilizing chemical that is used inmultiple consumer products, cosmetics, medications (inhaled medicines, topical medicaments),[22–25] and multiple vaccines.[26] It has been implicated in nonimmunologic anaphylactoid reactions[23]; however, a PubMed search revealed no case reports of delayed cutaneous reactions to polysorbate 80.

Tufts Medical Center, Ohio State University, and the University of California San Diego PT to SSO 20% in petrolatum and sorbitan monooleate 5% in petrolatum in their standard series, the allergens are available Chemotechnique Diagnostics (Vellinge, Sweden) and SmartPractice Canada.[21] The American Contact Dermatitis Society includes SSO in 20% petrolatum as an allergen to consider. Polysorbate 80 in 5.0% and 10% petrolatum is available for PT from Chemotechnique Diagnostics and SmartPractice Canada, respectively. There is no polysorbate 20 PT allergen commercially available, and no protocols were found on a PubMed search. Polysorbate in vaccines commercially available in the United States are listed in Table 2. A PubMed search for delayed cutaneous reactions among other COVID-19 vaccine excipients revealed no significant reports of delayed cutaneous reactions except for citric acid and tromethamine (trometamol).[27,28]

OTHER VACCINE COMPONENTS

Formaldehyde

Formaldehyde is a widely used preservative in commercial and personal care products due to its antimicrobial properties; it is commonly listed as one of the top 20 positive allergens on PT and was the American Contact Dermatitis Society contact allergen of the year in 2015.[29] Formaldehyde is contained in many vaccines, including the influenza vaccine[30]; cosmetics and personal care products (hair straightening, nail polish); permanent press textiles; metal working fluids; plastics, gloves, glues, and paints; and tissue specimens and cadaver preservation.[31] PT to formaldehyde is performed with a concentration of 1–2% in water with readings 48 hours and 72–96 hours after placement. Because formaldehyde and formaldehyde releasers are ubiquitous, knowledge of an formaldehyde allergy can impact quality of life in situations unrelated to vaccination and thus PT should be entertained, particularly, if the patient is symptomatic. There is a published report of patient who developed an erythematous and vesicular eruption on the hands in association with the hepatitis B vaccine; the patient had a PT positive result to formaldehyde.[32] Subsequent doses of the vaccine caused less-severe symptoms of itch and rash to the hands.[32] In addition, a 48-year-old man developed a widespread rash to his chest, shoulders, antecubital fossa, and arms 48 hours after receiving an influenza vaccine (Agriflu-Novartis Pharmaceuticals Canada Inc., Dorval, Quebec City, Canada); he had a PT positive result to formaldehyde (1 and 2% concentrations) and to other formaldehyde-releasing preservatives.[33] There is one case of a 45-year-old woman who developed Sweet syndrome within 1 day of receiving the influenza vaccine; she was treated with corticosteroids and her symptoms resolved. This influenza vaccine contained formaldehyde and thimerosal.[34]

Thimerosal

Thimerosal is a preservative used in multidose vials of influenza vaccines to prevent bacterial growth.[5] There is a case report of a 39-year-old woman with asthma and allergic rhinoconjunctivitis who developed a widespread erythematous rash 8 hours after the influenza vaccine.[35] The patient had also developed eyelid dermatitis previously with a thimerosal-containing contact lens solutions.[35] The rash resolved with systemic corticosteroids. She had a PT positive result to thimerosal, a component of the vaccine, which suggested that it was the culprit allergen.[35] A 75-year-old man developed skin, ocular, and oral symptoms after receiving his seasonal influenza vaccine, which contained thimerosal and formalin.[36] He was diagnosed with Stevens-Johnson syndrome.[36] The PT results to formalin and thimerosal were negative to both.[36]

Table 2 **Polysorbate 20 and polysorbate 80 content in vaccines***

Vaccine	Contains Polysorbate 20	Contains Polysorbate 80
Adenovirus	No	No
Anthrax (Biothrax)	No	No
BCG (Tice)	No	No
Cholera (Vaxchora)	No	No
Dengue (Dengvaxia)	No	No
DT (Sanofi)	No	No
DTaP (Daptacel)	No	No
DTaP (Infanrix)	No	Yes
DTaP-IPV (Kinrix)	No	Yes
DTaP-IPV (Quadracel)	No	Yes
DTaP-HepB-IPV (Pediarix)	No	Yes
DTaP-IPV/Hib (Pentacel)	No	Yes
DTaP-IPV-Hib-HepB (Vaxelis)	No	Yes
Ebola Zaire (ERVEBO)	No	No
Hib (ActHIB)	No	No
Hib (Hiberix)	No	No
Hib (PedvaxHIB)	No	No
Hepatitis A (Havrix)	Yes	No
Hepatitis A (Vaqta)	No	No
Hepatitis B (Engerix-B)	No	No
Hepatitis B (Recombivax)	No	No
Hepatitis B (Heplisav-B)	No	Yes
Hepatitis A/Hep B (Twinrix)	Yes	No
HPV (Gardasil 9)	No	Yes
Influenza, quadrivalent (Afluria)	No	No
Influenza (Fluad)	No	Yes
Influenza, quadrivalent (Fluvarix)	No	Yes
Influenza, quadrivalent (Flublok)	Yes	No
Influenza, quadrivalent (Fluelvax)	No	Yes
Influenza, quadrivalent (Flulaval)	No	Yes
Influenza, quadrivalent (Fluzone)	No	No
Influenza, high dose (Fluzone)	No	No
Influenza, quadrivalent (Flumist)	No	No
Japanese encephalitis (Ixiaro)	No	No
Meningococcal (MenACWY-Menactra)	No	No
Meningococcal (MenACWY-Menveo)	No	No
Meningococcal (MenB-Bexsero)	No	No
Meningococcal (MenB-Trumenba)	No	Yes
MMR (MMR-II)	No	No
MMRV (frozen: recombinant albumin) (ProQuad)	No	No
MMRV (frozen: human serum albumin) (ProQuad)	No	No
MMRV (refrigerator stable) (ProQuad)	No	No
Pneumococcal (PCV13-Prevnar 13)	No	Yes
Pneumococcal (PPSV-23-Pneumovax)	No	No
Polio (IPV-Ipol)	No	No
Rabies (Imovax)	No	No
Rabies (RabAvert)	No	No
Rotavirus (Rota Teq)	No	Yes
Rotavirus (Rotarix)	No	No
Smallpox (vaccinia) (ACAM2000)	No	No
Td (Tenivac)	No	No

Table 2 **Continued**

Vaccine	Contains Polysorbate 20	Contains Polysorbate 80
Td (TDVAX)	No	No
Tdap (Adacel)	No	No
Tdap (Boostrix)	No	Yes
Typhoid (Typhim Vi)	No	No
Typhoid (Vivotif Ty21a)	No	No
Varicella (frozen) (Varivax)	No	No
Varicella (refrigerator stable) (Varivax)	No	No
Yellow fever (YF VAX)	No	No
Zoster (shingles) (refrigerator stable) (Zostavax)	No	No
Zoster (shingles) (Shingrix)	No	Yes

BCG = bacillus calmette-guerin; DT = Diphtheria Tetanus; DTaP = Diphtheria Tetanus acellular Pertussis; IPV = inactivated polio vaccine; Hep=hepatitis; Hib = Haemophilus influenzae type B vaccine; HPV = Human Papillomavirus; MMR = measles, mumps, rubella; MMRV = measles, mumps, rubella and varicella; Td = tetanus diphtheria; Tdap=tetanus diphtheria acellular pertussis
**Data were obtained from the cdc.gov[26] Vaccine Excipient Summary, Excipients Included in U.S. Vaccines, by Vaccine accessed July 15, 2021.*

The influenza multidose vaccines contain thimerosal at 0.01%, which equates to 50 μg of thimerosal per 0.5-mL dose.[37] Thimerosal is also found in ophthalmic products and cosmetics.[38] The most common presentation of thimerosal reactions (from nonvaccine products) include periorbital dermatitis from eye medications and cosmetics.[5] In the United States, all vaccines routinely recommended for children ages $\leq$ 6 years contain no thimerosal or only trace amounts ($\leq$1 μg of mercury per dose) due to the concern of mercury toxicity because thimerosal is composed of ethyl mercury. Most persons do not experience symptoms when given thimerosal in a vaccine, even those with a positive PT result; >90% of patients with thimerosal allergy tolerated an intramuscular injection with thimerosal and only 5% developed a local reaction.[39] In fact, neither local nor delayed-type reactions with thimerosal are contraindications to a vaccine that contains this preservative.[40] If needed, PT is performed with thimerosal in petrolatum (0.1%).

Antibiotics

Antibiotics are commonly found in vaccines to prevent contamination by bacteria during the manufacturing process. The most common antibiotics encountered in vaccinations are neomycin, gentamycin, and polymyxin B. Neomycin is the most-used topical antibiotic in the United States, and use on abraded and inflamed skin has been associated with the development of contact dermatitis.[41] Clinically, patients with neomycin sensitivity may display cross-reactivity with other related aminoglycoside antibiotics. Contact sensitivity to neomycin is not a contraindication to vaccination.[42] Neomycin is a component in multiple vaccines, including the combination diptheria, tetanus, acellular pertussis-inactivated poliovirus vaccine (DTaP-IPV) combination vaccines, measles, mumps, rubella (MMR), rabies, varicella, influenza, and hepatitis vaccines.[26] Neomycin sulfate 20% in petrolatum is commercially available for PT.

Gentamicin is found in some traditional influenza vaccines.[26] Polymyxin B can be found in trace amounts in some influenza vaccinations, smallpox vaccines, polio vaccines, and topical medications.[24] A PubMed search did not reveal any cases of delayed reactions to vaccines due to polymyxin B or gentamicin. Polymyxin B and gentamicin are also encountered in topical creams, ointments, and eye and ear drops. Contact dermatitis to polymyxin B is most seen in patients with venous stasis ulcers.[43] PT for gentamicin is available at 20% in petrolatum and, for polymyxin B, at 3% in petrolatum. Other antimicrobials that have been used in vaccine development include tetracycline and streptomycin. Topical tetracycline derivatives have been implicated in eczematous contact allergy.[43] Streptomycin has been associated with eczematous contact dermatitis in health-care workers who have handled streptomycin.[43] PT is available with tetracycline 5% in petrolatum and streptomycin 2.5% in aqueous solution.[43] A PubMed search did not reveal any reports of delayed vaccine reactions due to tetracycline or streptomycin. When patch testing to antibiotics, particularly neomycin, a delayed reading is recommended.[44–45]

Aluminum

Aluminum is used as an adjuvant in vaccinations, including the diphtheria-tetanus-acellular pertussis vaccines, hepatitis A and B vaccines, pneumococcal and meningococcal conjugate vaccines, to enhance the immune response.[46] It may be found as aluminum hydroxide, aluminum potassium, or aluminum phosphate.[3] Contact allergy to aluminum has been

seen in patients who developed dermatitis to aluminum-containing antiperspirants and sunscreens.[3] Most reactions to aluminum in vaccines consist of painful and itchy persistent nodules at the injection site.[3,8] These nodules may develop days to months or even later.[47] Itch and associated skin changes, including eczema, hypertrichosis, and hyperpigmentation, can be seen; these nodules may flare with infections.[46] The nodules eventually disappear and the patient becomes asymptomatic.[46] A deep intramuscular injection may lessen the risk of a local reaction because longer needle lengths are associated with a lower rate of local reactions.[8,48] Others advocate waiting a period of 6–12 months because the risk for new granulomas decreases with time, especially if the patient's initial symptoms have already resolved.[8,46] PT is performed with aluminum chloride hexahydrate 2% in petrolatum or in aluminum hydroxide 10% in petrolatum;[8,49] some advocate[49] using aluminum chloride hexahydrate at 10% petrolatum to obtain more positive PT results. PT to metals requires an additional delayed reading after 5 days.[44]

Gelatin

Gelatin, an animal protein, is used in foods and medications, including vaccines.[5] It is used as a stabilizing vehicle in vaccines, including MMR, rabies, typhoid, yellow fever, shingles zoster, and varicella zoster,[5] and is an established cause of immunoglobulin E (IgE) mediated reactions to these vaccines.[50] Gelatin has been associated with systemic cutaneous delayed allergic reactions to varicella and Japanese encephalitis vaccines, and both IgG and IgE antibodies to gelatin have been implicated.[51,52] T-cell responses have been implicated in delayed reactions to MMR vaccine.[53] Immune complexes have also been proposed as a possible mechanism of cutaneous systemic reactions to gelatin.[54]

Phenoxyethanol

A preservative, 2-phenoxyethanol, is found in cosmetics as well as vaccines, including the diptheria-tetanus acellular pertussis vaccine.[5,26] A recent safety review of phenoxyethanol in cosmetics revealed rare sensitizing reports.[55] There is one case report in the literature of a toddler who developed widespread eczematous dermatitis after vaccination with Diphtheria Pertussis Tetanus in which 2-phenoxyethanol was implicated.[56]

Latex

Latex is found in the stoppers and syringe plungers of some vaccine vials. Reactions to latex can be divided into immediate-type symptoms due to IgE to *Hevea brasiliensis* and delayed cutaneous reactions to the accelerants and oxidants used in creation of rubber products (thiurams, carbamates, benzothiazoles).[57,58] The use of natural rubber latex is decreasing, and this is a rare cause of delayed reactions to vaccines.[58–60]

EVALUATION

Because patients with a history of DTHR to vaccines may perceive risk with subsequent reactions, they may choose to delay or skip subsequent vaccinations. Consultation and evaluation by a health-care provider, including an allergist/immunologist or dermatologist, can be helpful to prevent incomplete vaccination in these patients. In the patient with a history of DTHR to a vaccine, obtaining the relevant history and determining the severity of the reaction are important first steps. PT is suggested in patients with a history of nodule formation or contact dermatitis reactions and that those with local reactions do not have the need for evaluation.[5]

In patients with delayed cutaneous reactions, consider PT, while bearing in mind the patient's preferences, the feasibility of PT, and availability of vaccine components for PT. If positive, PT can aid in selecting a vaccine that does not contain that component. A thorough review of PT is beyond the scope of this article; however, epicutaneous PT is considered the criterion standard for the diagnosis of allergic contact dermatitis.[43] It is important to note that many of the selected reports discussed in this article are single case reports or contain a small numbers of participants and that data on sensitivity, specificity, and positive and negative predictive values are lacking. The relevance to a positive result on PT is ascertained *via* a correlation with known exposures, symptoms with the use of the allergen, and improvement with the avoidance of the positive PT allergen, which grants validity to the result.[43]

Performing PT can have an impact beyond vaccination because many vaccine components are contact allergens encountered in daily life. It has been shown that PT improves quality of life[61]; the identification and avoidance of relevant allergens improve the prognosis of allergic contact dermatitis.[62] No reports of PT with vaccines themselves were found in a PubMed search but protocols to patients who had PT and with a history of delayed vaccine reactions have been published.[57] Some vaccine components are available as standardized PT allergens. Micheletti *et al*.[57] developed a panel of 10 vaccine components used in PTs of such patients. Their panel includes 5% polysorbate 80, 0.1% thimerosal, 1% formaldehyde, 10% kanamycin sulphate, 3% polymyxin B sulphate, 5% streptomycin sulphate, and 25% gentamycin sulphate (F.I.R.M.A. SpA, Florence, Italy); and 1% phenoxyethanol, 10% aluminum, and 20% neomycin sulphate.[57] Of 173 patients had PTs with this panel, 49 had a positive PT result and were either directed to receive an alternative brand, if available, for subsequent vaccination, or

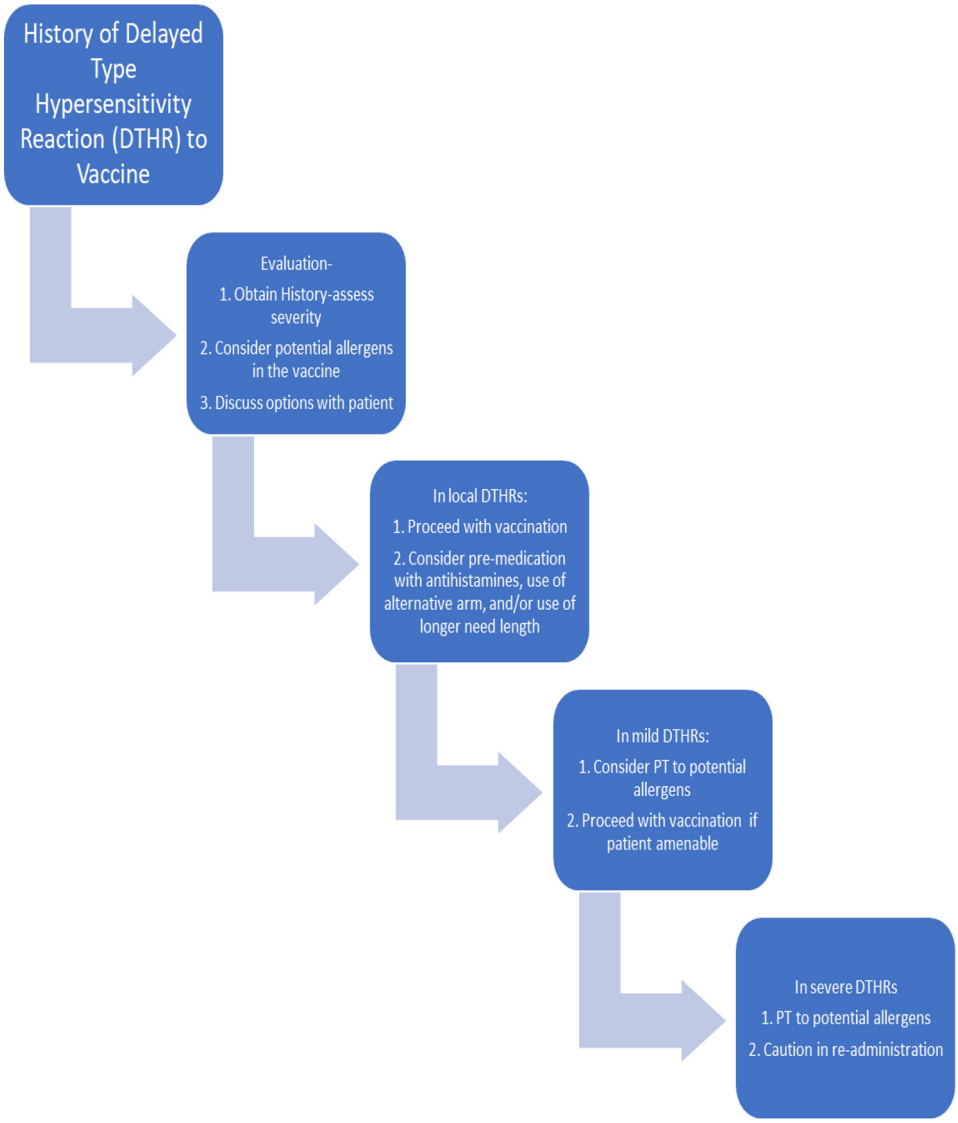

Figure 2. *Suggested algorithm for the evaluation and management of delayed-type hypersensitivity reactions (DHTR).*

received a subsequent dose of the original culprit vaccine after informed consent and discussion of the low risk of immediate-type hypersensitivity or anaphylaxis.[57] A proposed algorithm for evaluation of DTHR to vaccines is contained in Fig. 2.

MANAGEMENT

Because the majority of patients with DTHRs have had a local reaction, proceeding with vaccination after discussion with the patient is a suitable option. Measures such as premedication with antihistamines, use of the alternative arm for the vaccine, and/or use of a longer needle length can be considered, although the evidence for these measures is anecdotal and limited. A brief period of observation in the office after vaccination may also be considered; however, most delayed reactions will occur hours to days later. In patients with mild DTHRs and a negative PT result or if PT has not been performed, a discussion of the risk and benefit with the patient that focuses on the patient's preferences, importance of subsequent vaccination, and the presence of immunity to the pathogen on blood work will aid in future decisions. If an alternative vaccine without the suspected component is not available, then proceeding with vaccination in patients who have had a mild reaction and after shared decision-making with the patient is used is a reasonable option. We recommend extreme caution in vaccine readministration in cases of severe, delayed cutaneous reactions (serum sickness–like reactions, acute generalized exanthematous pustulosis, Sweet syndrome, Steven's Johnson/toxic epidermal necrolysis [SJS/TEN]) to vaccines In our opinion, deferring vaccination should be the last resort or applicable in small numbers of patients who present with DTHRs. Use of

shared decision-making with the patient can lead to highly satisfactory outcomes. Overall, the prognosis for patients who successfully receive subsequent doses of a particular vaccine is high.

CONCLUSION

Delayed reactions to vaccines are not uncommon. Knowledge of the components of vaccines allows for the assessment of potentially causative agents in delayed vaccine reactions. PT can be used to confirm suspicious agents. Allergen identification can help with avoidance and finding alternatives if the reaction was particularly burdensome or severe. Nonetheless, the majority of delayed reactions to vaccines are not a contraindication to further vaccine administration. Furthermore, knowledge of the most likely etiologic component can be useful in counseling patients with regard to future risk and may help with vaccination uptake.

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